PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/41, C07D 249/08, 249/16, 249/22 — A2

(11) International Publication Number: **WO 98/55118**

(43) International Publication Date: 10 December 1998 (10.12.98)

(21) International Application Number: PCT/EP98/03497

(22) International Filing Date: 4 June 1998 (04.06.98)

(30) Priority Data:
MI97A001329 5 June 1997 (05.06.97) IT

(71) Applicant *(for all designated States except US)*: IRILAB LTD. [IE/IE]; Merchant's House, 27/30 Merchant's Quay, Dublin 8 (IE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: ROSSI, Carla [IT/IT]; Via Cadore, 15, I–20135 Milano (IT).

(74) Agent: TRUPIANO, Roberto; Brevetti Europa S.r.l., Piazza Bernini, 6, I–20133 Milano (IT).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: USE OF NITROGEN HETEROCYCLIC AROMATIC DERIVATIVES IN THE TOPICAL TREATMENT OF THE EPITHELIAL TISSUES DISEASES

(57) Abstract

Derivatives of general chemical formula (I) and (IV) are advantageously used in the topic treatment of the diseases of the epithelial tissues, like the psoriasis (epidermis) and the ulcerous cholitis (low intestine). The mentioned derivatives display a high efficacy when administered for example by epicutaneous route in the case of dermatological illnesses like the psoriasis, atopic dermatitis and other similar affections, or when administered by oral or for example by rectal route in the case of diseases of the epithelia of the low intestine like the ulcerous cholitis and the Crohn.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

USE OF NITROGEN HETEROCYCLIC AROMATIC DERIVATIVES IN THE TOPICAL TREATMENT OF THE EPITHELIAL TISSUES DISEASES

OBJECT OF THE PRESENT INVENTION

Objects of the present invention is the use of nitrogen heterocyclic aromatic derivatives in the topical treatment of the diseases of the epithelial tissues.

Object of the present invention is also a chemical class of nitrogen heterocyclic aromatic derivatives and a procedure for their preparation.

Object of the present invention are pharmaceutical preparations which contains, as active principle, heterocyclic aromatic derivatives and their use in the topical treatment of the diseases of the epithelial tissues.

STATUS OF THE TECHNIQUE

Among all the diseases of the epithelial tissues, (epidermis, intestinal and bronchi mucosae), some of the more studied, because they large diffusion, are surely the psoriasis (epidermis) and the ulcerous cholitis (low intestine).

The psoriasis is a skin disease of genetic origin (phenotypes HLA with HLA-cw6 antigen) multi-factorial, characterised by inflammation and hyper-plasia of the epidermis with consequent plaques formation. In the psoriasis lesions, the rate of cell proliferation is of at least 10 times higher than normal. Different hypotheses exist on the origin of dermatological

diseases like psoriasis; one of this suggests that a primary defect in keratinocyte growth regulation in the germinative stratum, may lead to epidermis hyper-proliferation. This hypothesis has been recently supported by finding showing the involvement of cytokines (interleukin, interferon, growth factors including EGF) in its pathogenesis.

The anti-proliferative and inflammatory components of psoriasis need for a therapeutic approach which can affect both or at least one of the two mechanisms; from a practical viewpoint, depending on the severity of the pathology, the pharmacological and/or physical treatment is strengthen while the therapeutic index is reduced and the untoward effects increased.

It is a fact that, by increasing the severity and recrudescence of the disease, the therapies at present considered more effective and of large use start with topical treatments by emollients and keratolytic, then with tars, topical corticosteroids, antralins, antimicrobics, UVB applications combined with Goeckmen Ingram, photochemio therapy PUVA, until to use systemic treatments like oral corticosteroids, retinoids, metotrexate, hydroxyurea, cyclosporine.

When both topical pharmacological and physical therapies, including the use of PUVA (induction of the covalent binding of psoralens with the pyrimidinic

bases of DNA) result ineffective, the systemic therapies remain the only available. These are however performed by utilising drugs of high general toxicity but not always effective, like corticosteroids, retinoids, chemotherapics and cyclosporine.

When the therapeutic index is considered the results obtained are often poor whereas the recrudescence of the illness is rapid.

Therefore, the compounds nowadays used in the therapy of psoriasis are scarcely effective and produce several and severe side-effects.

Similarly, about 20% of all the inflammatory diseases of the low intestine including the Crohn illness, do not improve by the most commonly used anti-inflammatory therapies with 5-amino-salycilic acid and cortico-steroids, while need of more aggressive treatments with immuno-suppressants. Among these latter, azathiopirine and methotrexate are used, in spite of their cytotoxic activity leading in the course of prolonged therapeutic cycles to serious adverse events as pancreatitis, bone marrow depression, hepatitis and allergic reactions.

Therefore, the availability of non-cytotoxic drugs, endowed with a high anti-proliferative activity attained locally on the epithelia of the intestinal mucosae, is to be regarded as an useful progress in the therapy of severe diseases of the low intestine.

OBJECTIVES OF THE INVENTION

Objective of the present invention is to make available nitrogen heterocyclic aromatic derivatives to be used in the topical pharmacological treatment of diseases of epithelial tissues..

Objective of the present invention is also to make available nitrogen heterocyclic aromatic derivatives displaying their activity when topically administered by epicutaneous, oral or rectal route.

Objective of the present invention is also to make available pharmaceutical formulations, containing at least one nitrogen heterocyclic aromatic derivative as active principle, to be used in the treatment of diseases of the epithelial tissues, that display their activity when administered epicutaneously in the dermatological affections and by oral or rectal route in the diseases of the low intestine, that are well tolerated and able to allow a high therapeutic index.

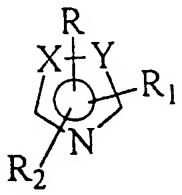
Objective of the present invention is also to make available nitrogen heterocyclic aromatic derivatives to be used in the treatment of diseases of the epithelial tissues and displaying a high activity when administered topically, thus able to reduce the risk of systemic side-effects.

Objective of the present invention is also to make available nitrogen heterocyclic aromatic derivatives to

be used in the treatment of diseases of the epithelial tissues in combination with other compounds also employed in the same therapeutic areas in order to achieve synergistic effects.

DESCRIPTION OF THE INVENTION

These and other objectives with further advantages which are clarified in the description below, are obtained by the nitrogen heterocyclic aromatic derivatives having the following general formula:



(I)

where:

-when X=Y, X, Y=N;

-when X=Y, X, Y=N, C, CH;

-R is chosen between:

hydrogen;

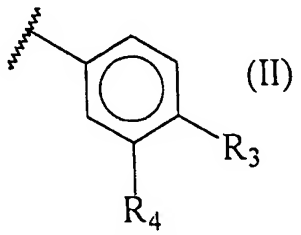
any group able to form a bond with a nitrogen atom,

$-COR_8$ where R_8 is C_1-C_{10} alkyl, C_2-C_4 alkenyl, C_2-C_4 alkinyl, phenyl possibly substituted by 1 to 3 substituents, benzyl, C_1-C_4 alkylamino, di-(C_1-C_4 alkyl)amino, phenylamino possibly substituted by 1 to 3 substituents, C_1-C_4 halolkyl, C_1-C_4 alkoxy, benzyloxy. Each eventual substituent being independently chosen

among: halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoro-methyl, CN, nitro, amino, di-(C_1-C_4 alkyl)amino, acyl-aminoC_2-C_4 and methylendioxy;

SO_2R_{12}, where R_{12} is chosen among: C_1-C_4 alkyl, phenyl, (C_1-C_4 alkyl)phenyl, (C_1-C_4 alkoxy)phenyl, acetyl-phenyl;

- R_1 has the following general formula:


(II)

where R_3 and R_4 are independently chosen among:

hydrogen,

halogen,

C_1-C_{10} alkyl or alkoxyl C_1-C_{10},

allyloxy, propergyloxy,

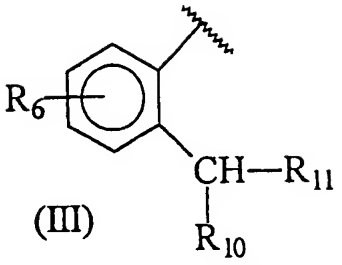
trifluoro-methyl,

phenyl,

di-methylamino,

or R_3 and R_4 together form a methylendioxy group;

- R_2 has the following general structure:



(III)

where R_6 is chosen among:

hydrogen,

halogen,

C_1-C_{10} alkyl or alkoxyl C_1-C_{10};

where R_{10} is chosen among:

hydrogen,

methyl;

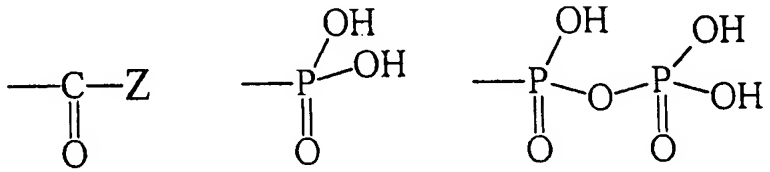
where R_{11} is chosen among:

hydrogen,

C_1-C_4 alkyl,

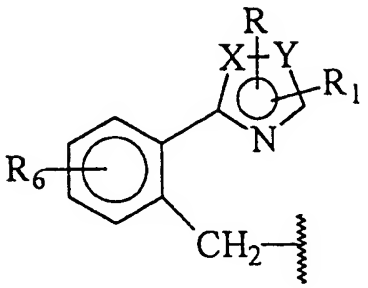
formyl,

OR_5, where R_5 is chosen among hydrogen, C_1-C_4 alkyl, SO_2R_{11}, where R_{11} is defined as above, or R_5 is chosen among:



where $Z=OR_7$ with R_7 is chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic

hydrocarbon, or is chosen according to the following formula:



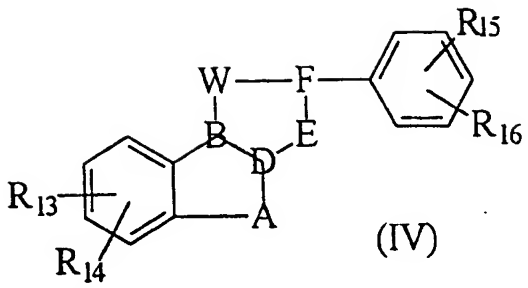
(XII)

where R, R_1, R_6, X and Y are defined as above or Z is chosen among C_1-C_{20} linear or branched alkyl, C_2-C_4 alkenyl, C_2-C_4 alkinyl, phenyl possibly substituted by 1 to 3 substituents, benzyl, C_1-C_4 alkylamino, di-(C_1-C_4 alkyl)amino, phenyl-amino possibly substituted by 1 to 3 substituents, C_1-C_4 halo-alkyl, C_1-C_4 alkoxy, benzyloxy. Each eventual substituent being independently chosen among: halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoro-methyl, CN, nitro, amino, di-(C_1-C_4 alkyl)amino, acyl-aminoC_2-C_4 and methylendioxy;

or Z is chosen equal to NHR_9 where R_9 is a linear or branched C_1-C_{20} alkyl chain, or mentioned R_{10} and R_{11}, together form a further bond between the carbon atom and one oxygen atom;

mentioned R_1 and R_2 are never located on two adjacent atoms of the heterocyclic aromatic ring;

or by nitrogen heterocyclic aromatic derivatives of general formula as follows:



(IV)

where:

-R_{15} and R_{16} are chosen among:

hydrogen,

phenyl,

hydroxy,

C_1-C_4 alkyl,

C_1-C_4 alkoxy,

C_3-C_5 alkenyloxy,

C_3-C_5 alkenyloxy,

C_3-C_6 ciclo-alkyloxy,

benzyloxy,

halogens,

or R_{15} and R_{16} together form a methylendioxy group;

-R_{13} and R_{14} are chosen among:

hydrogen,

halogens,

C_1-C_4 alkoxy;

-A is chosen as:

$-CH_2-$, $-CH=CH-$, $-CH_2-CH_2-$, $-(CH_2)_3$, $-CH_2-S-$;

-B is chosen as : C, N;

-D is chosen as: C, N;

or B and D together are equal to -C=C-;

-E is chosen as: N, C, CO, NH, CH, NR_{17}, CR_{17} where R_{17} is chosen as a linear C_1-C_4 alkyl;

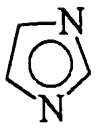
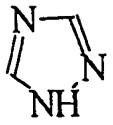
-F is chosen as: CH, N;

-W is chosen as: N, NH, CH, NR_{17}, CR_{17}, CR_{18}, where CR_{17} is defined as above and R_{18} is chosen as carboxy, carbo(C_1-C_4 alkyl), carbamyl, mono or di-(C_1-C_4 alkyl)carbamyl, hydroxymethyl;

The mentioned derivatives of general formulas (I) and (IV) being used in the topical pharmacological treatment of diseases of epithelial tissues.

According to the present invention, the term saturated or non-saturated aliphatic hydrocarbon means a linear or branched alkyl, alkenyl or alkinyl chain which contains one or more double or triple bonds. Always according to the present invention, the term alkyl or alkoxyl means a linear or branched alkyl or alkoxyl group.

Namely, the mentioned nitrogen heterocyclic aromatic derivative of formula (I) is a derivative of pyrazole, imidazole and 1H-1, 2, 4-triazole respectively:

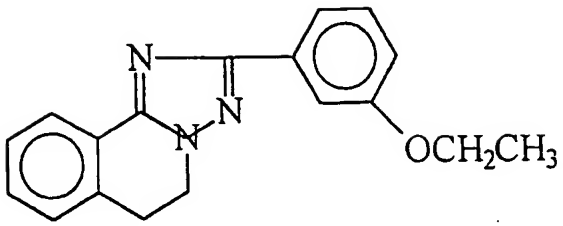




Of particular interest are those derivatives of formula (IV) where:

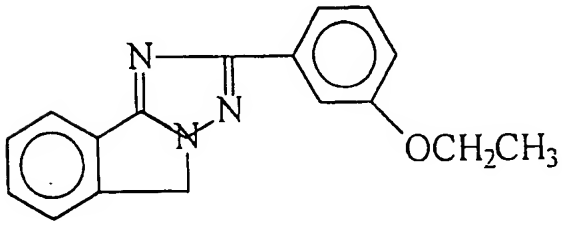
R_{13} and R_{14} is hydrogen, A is chosen among $-CH_2-$, $-CH=CH-$, $-CH_2-CH_2-$; D is chosen as N, B is chosen equal to C, W is chosen as N, R_{15} is hydrogen, and R_{16} is chosen between C_1-C_4 alkoxy and phenyl.

Derivatives of general chemical formula (I) and (IV) according to the present invention are advantageously used in the topic treatment of the diseases of the epithelial tissues, like the psoriasis and atopic dermatitis (epidermis) and the ulcerous cholitis (low intestine) or when administered by oral or for example by rectal route in the case of diseases of the epithelia of the low intestine like the ulcerous cholitis and the Crohn illness

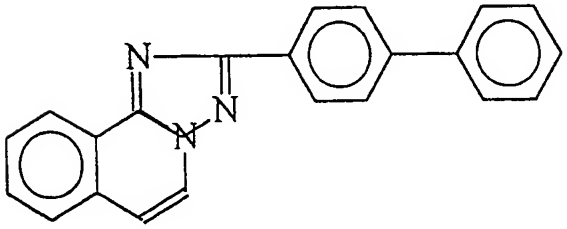
Namely, according to the present invention, of particular interest were those derivatives having formulas derived from general structures (I) and (IV), as follows:



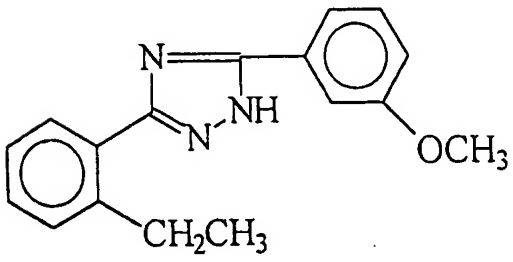
(X)



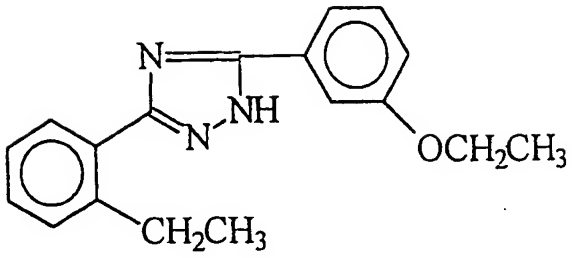
(XI)



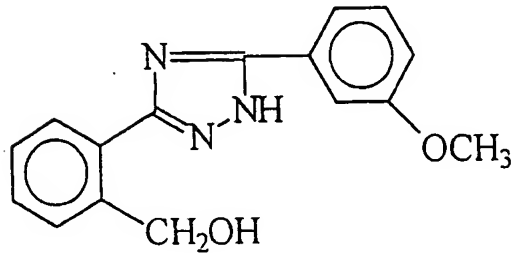
(XII)



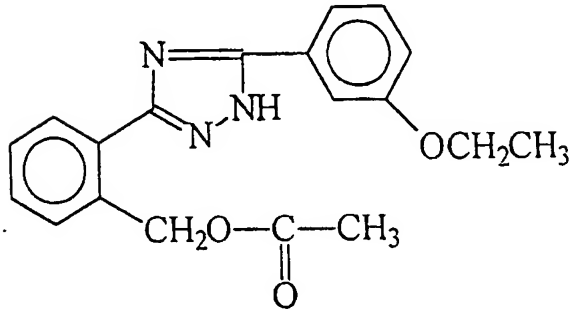
(XIII)



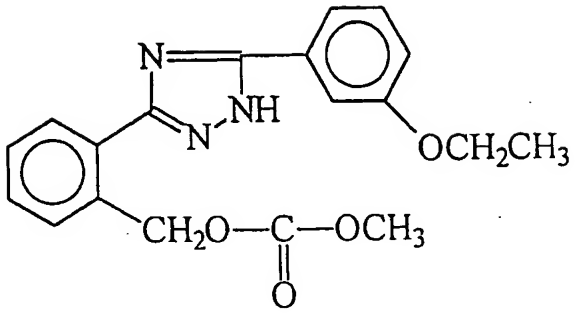
(V)



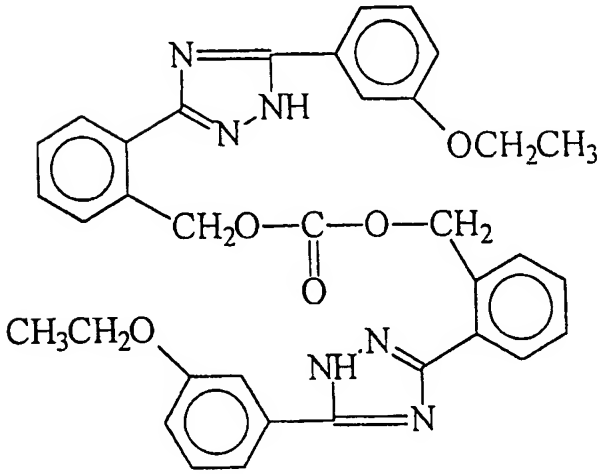
(VI)



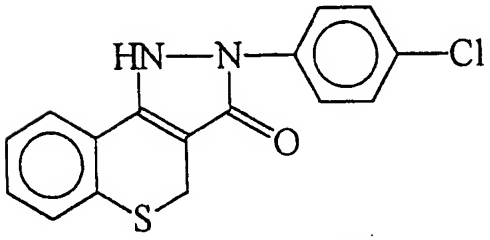
(VII)



(VIII)



(IX)



(XIV)

According to the present invention, of particular interest were derivatives of formula (I) where:

-when X=Y, X,Y=N;

-when X=Y, X,Y=N, C, CH;

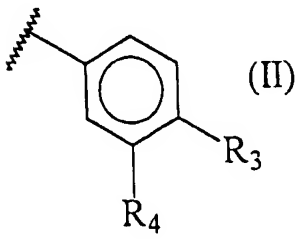
-R is chosen among:

hydrogen,

any group able to form a bond with a nitrogen atom,

$-COR_8$ where R_8 is a saturated or non-saturated C_1-C_{10} aliphatic hydrocarbon;

.-R_1 has the following general structure:



(II)

where:

R_3 and R_4 are selected among

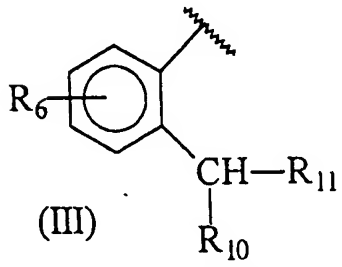
hydrogen,

halogen,

C_1-C_{10} alkyl or alkoxyl C_1-C_{10},

or R_3 and R_4 together form a methylendioxy group;

.-R_2 has the following general structure:



(III)

where R_6 is chosen among:

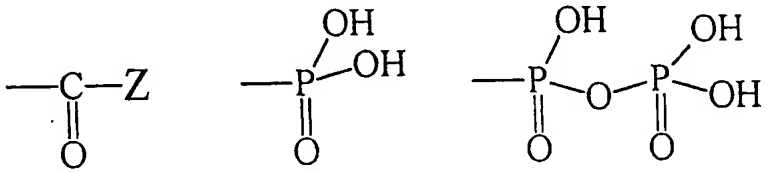
hydrogen,

halogen,

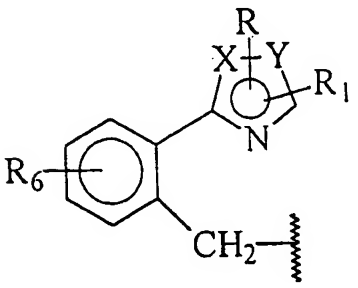
C_1-C_{10} alkyl or C_1-C_{10} alkoxyl;

where R_{10} is chosen as hydrogen,

where R_{11} is chosen as:OR_5, where R_5 is chosen among C_1-C_{20} saturated or non-saturated, linear or branched aliphatic hydrocarbon, or R_5 is chosen among:



where $Z=OR_7$ with R_7 chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, or is chosen according to the following formula:



(XII)

where R, R_1, R_6, X and Y are defined as above or Z is chosen equal to NHR_9 where R_9 is a C_1-C_{20} linear or branched alkyl chain.

Mentioned R_1 and R_2 being never located on two adjacent atoms of the heterocyclic aromatic ring.

The derivatives of the present invention, when administered topically by epicutaneous, oral route, at

doses much lower than those toxic or able to induce not desired side-effects, were shown to be highly effective in those therapies used to treat dermatological illnesses as for example the psoriasis and the atopic dermatitis as well as in the therapy of diseases of the epithelial mucosae of the low intestine.

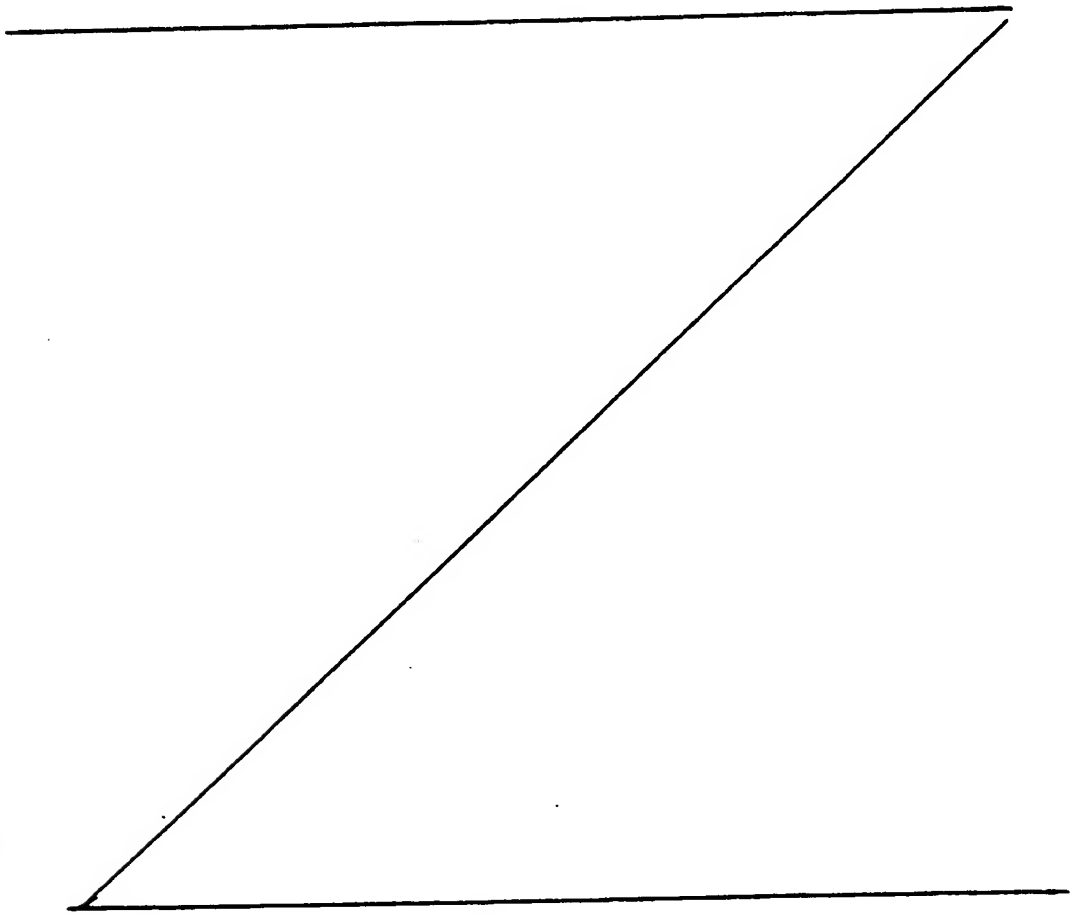
The derivatives of the present invention displayed a high efficacy when administered by topical routes, thus their use in the treatment of skin diseases and of the intestinal mucosae, and namely in the therapy of psoriasis or of the ulcerous cholitis, allows to markedly reduce the risk of systemic untoward effects.

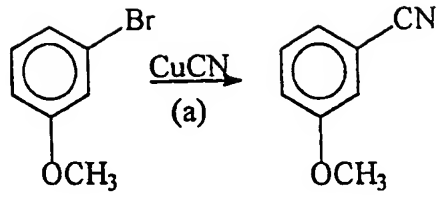
Apropos it has to be outlined as some of the compounds of the present invention when tested as anti-fertility agents display by oral route an activity much lower than that observed after parenteral injection, see Galliani et al., J.Pharm.Dyn. 5, 55-61 (1982). This finding, however, rather than to a low absorption is related to a rapid and extensive hepatic first-pass effect leading to the formation of inactive metabolites, see Assandri et al., Reviews on Drug Met, & Drug Interactions, IV, 237-261 (1982); A.Assandri et al., Xenobiotica 14, 429-443 (1984). This behaviour, due to the limitation of systemic toxic effects, becomes useful in the topical treatment of both dermatological and intestinal diseases. In addition

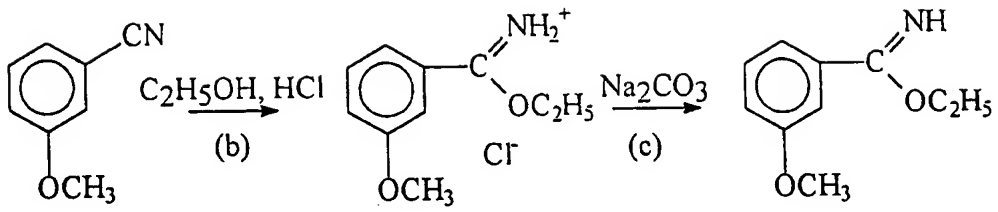
since the derivatives of the present invention display their activity through a mechanism, not yet clarified, but very likely different from that of other drugs currently used in the therapy of psoriasis and of the ulcerous cholitis, they can be advantageously used in combination so to give rise to synergistic responses.

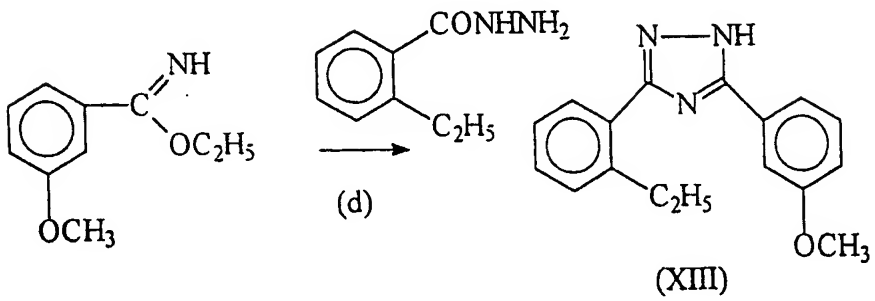
Of particular interest, due to its high efficacy, is compound (XIII), which, for example, can be synthesised according to the following scheme:

Scheme 1









(XIII)

Example 1

(a) 3-METHOXY BENZONITRILE. 3-bromoanysole (210 mg, 1.12 mmoles) and CuCN (93.14 mg, 1.04 mmoles) were dissolved in N-methyl pyrrolidone (5 mL) and the reaction mixture is warmed to 220°C for 2 hours. After cooling to 50°C, the reaction mixture was added both 6mL of an aqueous solution containing 400 mg of $FeCl_3.6H_2O$ and 0.6 mL 37% HCl, then was maintained

under stirring at 65°C for 20 min. After addition of 20 mL water the raw product was extracted by ethyl ether (5x20 mL); the organic phase de-hydrated by Na_2SO_4, was dried giving 114.3 mg of the crude compound (93.4%).

(b), (c) ETHYL ETHER OF THE 3-METHOXYBENZOIMIDIC ACID. Crude 3-Methoxy benzonitrile (114.3 mg) dissolved into anhydrous ethyl ether (3 mL) and anhydrous ethanol (0.15 mL), was cooled to 4°C; anhydrous HCl is then bubbled for 7 hours. After one night at 4°C, the intermediate precipitate (hydrochloride salt) was taken up with 8% Na_2CO_3 in water (4 mL) and extracted with ethyl ether (5 x 10 mL). Na_2SO_4 was added to the organic phase, and after filtration the solution was evaporated to dryness to give 85 mg of immino ether (44.65%).

(d) 3-(2-ETHYLPHENYL)-5-(3-METHOXYPHENYL)-1h-1, 2, 4 TRIAZOLE (XIII).

A mixture of immino ether (85 mg, 0.474 mmoles) and 2-ethyl benzo-hydrazide (164 mg, 1 mmole) in acetonitrile (0.5 mL), was warmed under reflux. After 1 hour stirring, solvent was distilled and substituted by 2-ethoxyethanol (0.6 mL). The reaction mixture was refluxed for 3 hours, the solvent evaporated under vacuum and the residue, re-dissolved in CH_2Cl_2 (2 mL), was chromatographed on a silica gel column (10 g). As

elution solvents, mixtures of CH_2Cl_2 and $CH_3COOC_2H_5$ in varying proportion (99:1 to 95:5) were used. Fractions containing the desired product were collected, solvent evaporated to give 96,27 mg (72.6%) of compound (XIII).

Of particular interest, was compound (XIV), which, can be synthesised according to the procedure hereafter reported in example 2.

Example 2:

A mixture containing 60 g (0.270 moles) of 3-carbomethoxy-4-thio-cromanone (T. Moriwake, J:Med. Chem. 9, 163 (1966), 42.4 g (o,297 moles) of p-chlorphenyl-hydrazine and 18 mL of acetic acid, was warmed in an oil bath, under nitrogen atmosphere at 115°C for 30 min. The resulting solid yellow precipitate was heated further at 180°C for 1.5 hours, then cooled and the excess of acetic acid eliminated under vacuum. The semi-solid residue was repeatedly disintegrated into large ether volumes while each time the suspension was filtered. The crude product (71g) was dissolved in 3 L of iso-propanol, concentrated to 1.% L and cooled to give 54 g (64%) of compound (XIV).

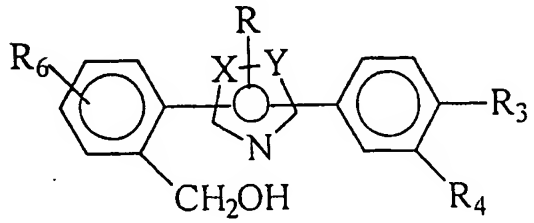
Melting point: 235-237°C

IR 3.65 (br, NH), 6.12, 6.26, 7.63, 9.23, 12.1 nm.

MS: m/e 314 (calculated 314)

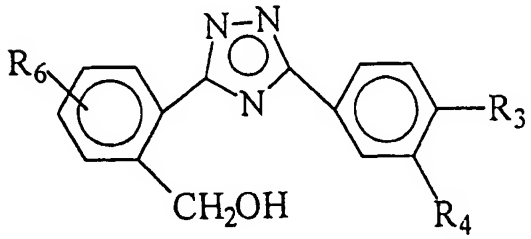
NMR (DMSO d_6): τ 6.0 (s, 2H, CH_2), 2.1-2.8 (m, 8H, aromatic protons).

The derivatives object of the present invention are , for example, advantageously prepared starting from a derivative (XV) with the following chemical formula:



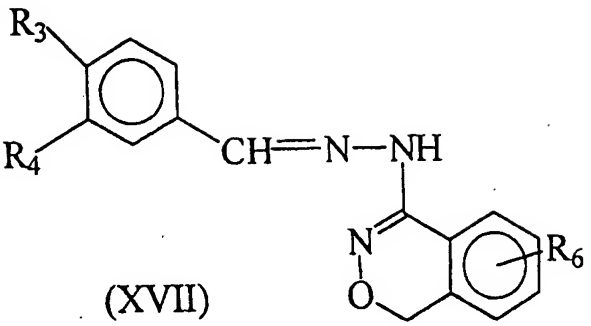
(XV)

More particularly, when substituents R_1 and R_2 are in position 3 and 5 respectively, the corresponding derivative (XI) has the following chemical formula:



(XVI)

The above mentioned derivative of formula (XVI), is prepared according to different procedures already reported by the literature and is described in EP11129. In this case the method consists in the rearrangement of hydrazones of substituited benzaldehydes with 4-hydrazino-1H-2,3-benzoxazines of formula (X)



(XVII)

wherein R_3, R_4 and R_6 are as defined as for the derivatives of formula (I).

This rearrangement simply occurs by refluxing the hydrazone III in a high boiling inert organic solvent, such as for instance, xylene, N,N-dimethylformamide, and halogenated aromatic hydrocarbons, for about 30 minutes and then recovering the compound II by filtration.

Another suitable method for the preparation of the 2-hydroxymethyl-phenyl derivatives of formula (XVI), consists in the oxidation of the corresponding 2-methylphenyl triazoles, either directly to the alcohol (XVI) or to the corresponding carboxylic acid followed by a reduction of this latter to the alcohol(XVI).

In the former case, ceric ammonium nitrate or silver (II)oxide are the oxidising agents which may be suitably employed, while in the latter, the oxidative step is carried out with any of the several oxidisers known in the art to transform a methyl group on an aromatic ring to a carboxylic group, such as permanganate, nitric acid, and dichromate, and the

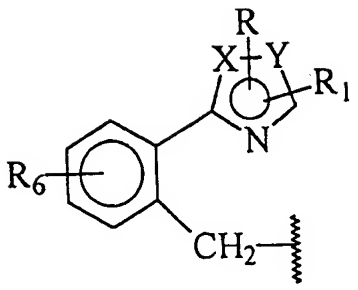
reductive step in easily performed with a metal hydride.

Alternatively, the starting compound of formula (XVI) can be prepared by following the process described in EP80053.

Also derivative (XVI) where R_6 and R_3 are hydrogens and R_4 is equal to OCH_2CH_3, is prepared according to Example 9 as reported below.

Referring to compounds of formula (I), object of the present invention, the procedure for their preparation starting from the corresponding derivative of formula (XV) varies depending whether the substituent R is hydrogen or a group R_8-CO wherein R_8 has the same meaning as above in relation to derivatives of formula (I).

When R is hydrogen, the derivative of formula (XV) is prepared according to different procedures already reported by the literature, in equimolar ratio with phosgene ($COCl_2$) and the resulting chloro-carbonate is left to react with a derivative Z where $Z=OR_7$ and R_7 is chosen among a saturated or non-saturated, linear or branched aliphatic hydrocarbon C_1-C_{20} , or is chosen according to the following formula:



(XII)

where R, R_1, R_6, X and Y are defined as above,or Z is chosen equal to NH-R9 where R_9 is a linear or branched C_1-C_{20} alkyl chain.

The derivative of formula (I) where R is chosen as hydrogen, can be successively separated from the possible by-products formed during the reaction with phosgene. Phosgene to use is commercially available already dissolved in appropriate solvents.

Alternatively, the derivative of formula (XV) can undergo reactions according to the following general scheme which alows preparation of symmetric and asymmetric carbonates, in detail:

⇒both for the intermediates preparation (alcoholate and imidazolide) and for the end carbonate product, an inert solvent is chosen, i.e. chloroform, dichloro-methane, tetrahydrofuran:

⇒alcoholate preparation is carried out on the selected alcohol using as base NaH or matallic Na either in catalytic or stoichiometric amounts, temperature can be between 0°C and 60°C (optimal room temperature),

while reaction time ranges between 30 min to 12 hours (optimal 1 hour);

⇒the synthesis of the imidazolide of the second alcohol is carried out using as reagent carbonyl-diimidazole with temperature between 0°C and 60°C (optimal, room temperature), while reaction time ranges between 30 min to 12 hours (optimal 1 hour);

⇒the synthesis of the end carbonates products is carried out by mixing properly the solutions of the alcoholate and of the imidazolide for a time of 6 to 24 hours (optimal 12 hours) at a temperature between 0°C and 60°C (optimal, room temperature).

Merely as an example, not limiting the present invention, a general method for the synthesis of derivatives of formula (I), is hereafter described:

Example 3

A 50 mL solution of 3-(2-(hydroxymethyl)phenyl)-5-(3-ethoxyphenyl)-1H-1, 2, 4 triazole (3g, 10 mmoles) in tetrahydrofuran, at room temperature, is added an 80% NaH suspension (310 mg, 10 mmoles) in tetrahydrofuran (50 mL). The reaction mixture is shacked at room temperature for 1 hour. The resulting solution is then added to a tetrahydrofuran solution containing the imidazolide of the selected alcohol obtained by reacting the alcoholic derivative (10 mmoles) with

1,1'-carbonyl-diimidazole (1.65 g, 10 mmoles) in tetrahydrofuran (20 mL) for 1 hour at room temperature. The mixture is stirred at room temperature for 12 hours, then solvent is take to dryness under vacuum and the residue re-dissolved in methylene chloride. The organic phase is washed with water, dried by anhydrous Na_2 SO_4 and evaporated under vacuum. The obtained crude material is purified by column chromatography on silica gel (eluent hexane-ethylacetate, 8:2, v/v). After evaporation of the solvents, the solid pure product obtained is re-dissolved in hexane, filtered and dried under vacuum.

The compounds described below were prepared according to the procedure reported in Example 3.

Example 4

Preparation of 3-(2-(ethoxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole

Yield 52%; melting point = 124-126°C

^{1}H-NMR: 7.98 (1H, t, J=4.1 Hz); 7.72-7.74 (6H, m); 7.06 (1H,d, J=6.9 Hz); 5.68 (2H, s); 4.16 (2H, q, J=7.0 Hz), 4.14 (2H, q, J=7.1 Hz); 1.40 (3H, t, J=7.0 Hz); 1.21 (3H, t, J=7.1 Hz).

^{13}C-NMR: 158.76, 154.21, 133.65, 129.83, 129.04, 128.77, 128.60 (2C), 118.16 (2C), 115.86, 112.04 (2C), 67.20, 63.33, 63.15, 14.36, 13.82.

Example 5

Preparation of 3-(2-(butoxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole.

Yield 58%; melting point= 119-121°C

^{1}H-NMR: 8.00 (1H, t, J=4.8 Hz); 7.70-7.40 (6H, m); 7.03 (1H,d, J=7.2 Hz); 5.62 (2H, s); 4.12 (2H, q, J=7.0 Hz), 4.03 (2H, t, J=6.4 Hz); 1.49 (2H, m); 1.36 (3H, t, J=7.0 Hz); 1.23 (2H, m); 0.80 (3H, t, J=7.3 Hz).

^{13}C-NMR: 158.70, 154.29, 133.51, 129.89, 129.20 (2C), 128.63 (2C), 128.35 (2C), 118.15 (2C), 115.96, 111.98 (2C), 67.27, 67.17, 63.20, 18.03,14.26, 12.98.

Example 6

Preparation of 3-(2-(hexyloxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole.

Yield 42%; melting point = 90-92°C

^{1}H-NMR: 8.07 (1H, m); 7.69-7.40 (6H, m); 7.06 (1H, d, J=7.3 Hz); 5.68 (2H, s); 4.15 (2H, q, J=7.0 Hz), 4.07 (2H, t, J=6.6 Hz); 1.56 (2H, m); 1.40 (3H, t, J=7.0 Hz); 1.23 (6H, m); 0.85 (3H, t, J=6.5 Hz).

^{13}C-NMR: 158.76, 154.29, 133.65, 129.79, 128.87 (2C), 128.59 (2C), 128.15 (2C), 118.15 (2C), 115.87, 112.03 (2C), 67.37, 67.29, 63.13, 30.49, 27.87, 24.52, 21.61,14.36, 13.43.

Example 7

Preparation of 3-(2-(octyloxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole.

Yield 49%; melting point= 86-89°C

^{1}H-NMR: 8.06 (1H, m); 7.72-7.40 (6H, m7); 7.05 (1H, d, J=7.1 Hz); 5.69 (2H, s); 4.15 (2H, q, J=7.0 Hz), 4.07 (2H, t, J=6.4 Hz); 1.56 (2H, m); 1.40 (3H, t, J=7.0 Hz); 1.23 (10H, m); 0.86 (3H, t, J=6.5 Hz).

^{13}C-NMR: 158.76, 154.28, 133.65, 129.77, 129.01, 128.84, 128.59 (2C), 128.59 (2C), 128.13 (2C), 118.16 (2C), 115.83, 112.03 (2C), 67.37, 67.30, 63.13, 30.88, 27.91, 24.89, 21.72,14.35, 13.53.

In the following example 6, the synthesis of one derivative of formula (I), where the group R_7 is chosen of formula (XII), symmetric carbonates, is described:

Example 8

Preparation of Di-(2-(5-(3-ethoxyphenyl)-1H-1, 2, 4-triazol-3-yl) phenylmethyl) carbonate.

A 15 mL solution of 3-(2-(hydroxymethyl)phenyl)-5-(3-ethoxyphenyl)-1H-1, 2, 4 triazole (0.7g, 2.4 mmoles) in tetrahydrofuran, at room temperature, is added a 80% NaH suspension (35 mg, 1.2 mmoles) in tetrahydrofuran (15 mL). The reaction mixture is shacked at room temperature for 1 hour. The resulting solution is then added 1,1'-carbonyl-diimidazole (192 mg, 1.2 mmoles) in tetrahydrofuran (20 mL) for 1 hour at room temperature. The mixture is stirred at room temperature

for 12 hours. Solvent is taken to dryness under vacuum and the residue re-dissolved in methylene chloride. The organic phase is washed with water, dried by anhydrous Na_2 SO_4 and evaporated under vacuum. The obtained crude material is purified by column chromatography on silica gel (eluent hexane-ethylacetate, 7:3, v/v). After evaporation of the solvents, the solid pure product obtained is re-dissolved in hexane, filtered and dried under vacuum. 212 mg of the compound (XVII) were obtained.

Yield 36%; melting point = 143-145°C

^{1}H-NMR: 8.07 (2H, m), 7.69-7.38 (12H, m); 7.03 (2H,d, J=8.4 Hz); 5.72 (4H, s); 4.12 (4H, q, J=7.0 Hz), 1.37 (6H, t, J=7.0 Hz);.

^{13}C-NMR: 158.74, 154.21, 133.59, 129.81 (2C), 128.97 (2C), 128.02 (2C), 118.18 (2C), 115.88, 112.00 (2C), 67.41, 63.13, 14.33.

Example 9

(a) 2-BENZOYLOXYMETHYL BENZOIC ACID

Phtalide (50g, o.37 moles) is dissolved in 20% NaOH (267 mL, 1.33 moles) by eating the mixture at 60°C. The resulting solution is diluted with water-ice (2.2 kg) and added,for 10 min under vigorous stirring, with benzoyl chloride (56 mL, 0.48 moles). After 1 hour the reaction mixture is dissolved with 4 L water, the pH

adjusted to 2.5 by 10 % HCl and the precipitate is filtered under vacuum. The solid is suspended into 600 mL of heat water (50°C), shacked for 5-10 min and re-filtered. The procedure is repeated four times. The crude compound is crystallised from ethanol/water 7:3 (200 mL).

Yield: 45 g

TLC: toluene:ethyl acetate: acetic acid, 5:5:0.1

(b) 2-BENZOYL-OXYMETHYL-BENZOIC ACID CHLORIDE

To the solution of the 2-benzoyloxymethyl benzoic acid (40 g, 0.15 moles) in chloroform (400 mL), anhydrous pyridine (0.92 mL, 4 mmoles) is added under stirring and thereafter, within 10 min, thionyl chloride (13.7 mL, 0.18 moles). The reaction mixture is refluxed for 1 hour then is take to dryness. The residue is re-dissolved in chloroform and re-dried. The operation is repeated another two times and the chloride obtained used .

(c) 2-BENZOYL-OXYMETHYL-BENZOIC ACID HYDRAZIDE

To the solution of 98% hydrazine hydrate (24 mL, 0.62 moles), in 95% ethanol (120 mL) cooled into an ice bath, a solution of the 2-benzoyloxymethyl benzoic acid chloride (0.15 moles)in methylene chloride (120 mL), is added drop wise. The reaction mixture is stirred at room temperature for 2 hours, the lower phase is

separated, and the upper phase is re-extracted by methylene chloride. The organic phases are poured and washed with NaCl saturated water and take to dryness. The residue is shelled into ethyl ether (500 mL), filtered and dried.

Yield: 36.5 g

TLC: toluene:ethyl acetate: acetic acid, 5:5:0.1

(d) 3-ETHOXY- ETHYL-BENZIMIDATE

To a mixture of 3-ethoxy benzonitrile (25 mL, 0.177 moles) and absolute ethanol (12.3 mL, 0.2 moles) cooled into an ice-bath, HCL gas is bubbled until saturation. After standing in refrigerator for 48 hour (the yield is increased by prolonging the standing period) the crude material is suspended in ethyl ether, filtered and dried.

Yield: 18 g

The ethoxy ethyl benzimidate chloride obtained is dissolved in water and alkalinised by 5% $NaHCO_3$. By extraction with 1, 1, 3 trichloro-ethane (200 mL) the ethoxy ethyl benzimidate base is obtained. The solution is dried to be used in the next step.

(e) 3-(2-BENZOYL-OXYMETHYL-PHENYL)-5-(O-ETHOXY-PHENYL)-1H-1, 2, 4 TRIAZOLE.

To the ethoxy ethyl benzimidate (base) solution (0.078 moles) in 1,1,3-trichloroethane from the previous step,

the hydrazide of 2-benzoyl-oxymethyl-benzoic acid (19.2 g, 0.071 moles) is added. The mixture is heated first at 90°C for 90 min then at 110+C for 1 hour, trichloroethane is distilled under vacuum until precipitation starts. Xilene (250 mL) is added and the solution is heated under reflux by eliminating the reaction water with Marcusson. After 1 hour the reaction mixture is cooled to room temperature, the precipitate filtered and dried under vacuum.

Yield: 20 g

TLC: toluene:ethyl acetate: acetic acid, 5:5:0.1

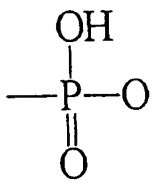
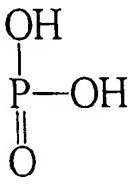
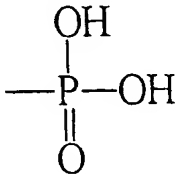
(f)3-(2-HYDROXY-METHYLPHENYL)-5-(ETHOXYPHENYL)-1H,1, 2, 4-TRIAZOLE

A solution of 3-(2-benzoyl.oxymethylphenyl)-5-(O-ethoxyphenyl)-1H, 1, 2, 4 triazole (20 g, 0,05 moles) in 10% NaOH (86 mL) and 95% ethanol (130 mL) is warmed for 1 hour at 70°C. Ethanol is then evaporated under vacuum and the aqueous solution left, diluted with water (130 ml) and cooled by a ice-bath, is adjusted to pH 8 with 10% HCl. The obtained suspension is stirred at room temperature for some hours, the solid is filtered, dried under vacuum and finally crystallised from ethanol (100 mL).

Yield: 11.8 g

When R is chosen equal to -CO R_8, where R_8 is a saturated or a non saturated C_1- C_{10} aliphatic hydrocarbon, the hydroxy group of derivative (XV), will be protected according to known methods. Protected derivative (XVb) will be also obtained and acylated according to known methods in order to introduce the -COR_8 group. Subsequently this acylated derivative will be de-protected and allowed to react with phosgene as reported above. In the case of X=Y=N, the acylation reaction could be carried out as described by EP80053.

When R_5 is chosen:

Derivatives of formula (I) are advantageously prepared starting from derivatives of formula (XV) (eventually submitted to a previous acylation reaction as already described) by reaction with phosphoric acid or equivalents according to known methods.

For derivatives of formula (I), when X=Y=N following the acylation procedure described above, both single compounds, where the substituent R is located on one of the two adjacent nitrogen atoms and mixtures of the two possible isomers can be obtained.

In this latter case, the mixture can be separated into the single components by chemico-physical known

methods. For example, the way a mixture can be resolved into the single components is a fractionated crystallisation, which take advantage of the different solubility of each compound in various solvents at different temperatures. Suitable solvents that can be used for this method are chosen as an example, among hexane, ethyl-acetate, C_1-C_4 alkyl ethers, methylen chloride, light petroleum ether and mixtures thereof.

A further illustrative example of a method useful for the separation of the isomers' mixture is based on column chromatography, performed on non-acid, buffered adsorbents, as silica-gel buffered to pH=7. Another example of a method useful for the separation of the isomer mixture is based on the use of preparative high pressure liquid chromatography (PHPLC), carried out on proper columns, for example filled with silica-gel esterified with octyl-silane or octyl-decylsilane. Other obvious procedures useful for resolving a mixture of isomers into the single components are intended to fall within the scopes of the invention.

As reported in the literature, see Potts K.T , J: Chem. Soc. 3451, (1954) and Potts K.T., Chem. Rew. 61, 99 (1961), Kubota and Uda, Chem. Pharm. Bull. 23(5), 955 (1975), due to the high mobility of the hydrogen atoms of !, 2, 4-triazoles, compounds of formula (I) of the present invention where X=Y=N, are to be regarded as a mixture of two tautomeric forms, i.e. those in which

the hydrogen atom is located on one or the other of the two adjacent nitrogen atoms of the triazole ring. Depending on the nature of the substitutes at the 3 and 5 positions, a form may predominate on the other one. Consequently, both mentioned tautomeric forms must be considered as part of the present invention. It is known that tautomeric forms rapidly exchange in between and consequently behave as a dynamic equilibrium.

Anyway, throughout the whole description and claims relative to the present invention, 3, 5 diphenyl-1H-1, 2, 4-triazoles according to the present invention, will be numbered as reported in the compounds described throughout the text.

The derivatives of general formula (IV) can be advantageously prepared as reported, for example, by GB 1479759 and GB 1484615.

It has been shown that the compounds of the present invention, do not retain hormonal or anti-hormonal or lympholytic activity; differently from the alkylating agents they inhibit the antibody formation versus corpuscular antigens (ram erythrocytes) when administered after the antigen; differently from anti-metabolites they are inactive in all the tumour models tested (leukemia P-388, L1210, EL(4) T, and the lymphoma 70(Z)B) made exception for the choriocarcinoma; Differently from cyclosporin A, they

do not exert a selective action on lymphocytes B and/or T. At last, the compounds of the present invention do not interfere with the macrophagic function and do not retain cytotoxic activity neither in in vivo or in vitro experimental models.

As already described, the derivatives of general chemical formula (I) and (IV) were shown effective in animal models predictive for anti-psoriasis and anti-ulcerous cholitis activity, whereas clinical studies did showed their effectiveness in the treatment of dermatological diseases as the psoriasis and atopic dermatitis.

Apropos, in an animal model predictive for the evaluation of an anti-psoriasis activity as reported by Lowe M.L., Drug Dev. Res. 13/2-3, 147-155 (1988), Gallado Torres H.I. et al., Phatobiology 63/6, 341-347 (1995), compounds of formula V, VI, VII, VIII, IX, X, XI, XII, XIII and XIV have been tested in mice where a chronic hyper-proliferative dermatitis, characterised by epidermic hyperplasia, was induced.

The results obtained show the high efficacy of the selected compounds in inhibiting differentiation and/or proliferation of degenerated epithelial cells. Inhibition of DNA synthesis of the epidermis of hairless mice 16 hours after the epicutaneuos treatment with compounds V and XIV.

The compounds were administered dissolved and/or suspended in sesame oil at the concentration of 0.25%.

COMPOUND	DNA 10% concentraton in tissue ± S.D.
Vehicle	115.2 ± 9.30
V	32.3 ± 6.4
VI	55.8 ± 9.2
VII	44.3 L 6.6
VIII	39.1 ± 5.7
IX	46.3 L 7.3
X	68.6 ± 9.4
XI	72.4 ± 10.1
XII	26.7 ± 4.5
XIII	48.3 ± 5.9
XIV	75.8 ± 8.8

Because of these results, the therapeutic activity of compound of formula XIII in the therapy of psoriasis, was evaluated as reported in the Example 10, as follows:

Example 10

In some patients observed individually and thereafter by a controlled study, the anti-psoriasis activity was evaluated according to an unbalanced, double-blind experimental design.

In detail, 18 male patients, aged more than 18 years, demonstrating at the physical examination and from the routine laboratory (haematology, blood chemistry, urinalysis) a general good health condition, having a severe chronic pathology characterised by large-plaques of *psoriasis vulgaris* involving an area between 10-20% of the whole body surface, previously unsuccessfully treated (at least 3 months before) with topical and systemic known therapies, have been enrolled and randomised in two-groups of 6 (control) and 12 (treated) units.

The treated group received compound XIII formulated as cream for topical use at the concentration of 0.1% (1 mg/g) once daily for 7 consecutive days, whereas the control group received, according to the same dose regime, placebo only.

The 8^{th} day, on three different lesions from different areas, an efficacy judgement, based on a semi-quantitative evaluation criteria of the erythema, was given by the dermatologist: 0= absent, 1= minimum, 2= moderate, 3= severe. These measures were then summarised in a global comparative evaluation: -1(worsening), 0= (no or minimum (10%) improvement), +1=

(moderate improvement, 11 to 50%), +2= (marked improvement, 51 to 99%) and +3 = complete recovery.

TABLE 1 -

VALUTATION OF CLINICAL EFFICAY IN COMPOUND (XIII) (0.1% cream) IN PATIENTS AFFECTED BY VULGARIS PSORIARIS TREATED BY EPICUTANEOUSLY 1xDIEx7 CONSEQUTIVE DAYS

CLINICAL RESPONSE	PLACEBO (N=6)	COMPOUND (XIII) (N=12)
worsening	2	0
none or minimum	4	0
moderate improvement	0	3
marketed improvement	0	7
recovery	0	2

All patients of the two experimental groups completed the study without the treatment give rise to untoward

local and/or systemic effects. The laboratory examinations, repeated within 7 days after the study end, did not show changes of clinical relevance of any of the parameters assayed.

Dealing with the activity of the compounds object of the present invention, on the inflammatory diseases of the low intestine, some compounds, namely V, VI, X and XI, were tested in animal models of ulcerous cholitis (Wallace J.L. et al.,Eur. J. Pharmacol. 257, 249 (1994); Renter B.K. et al. J. Clin. Invest. 98, 2076-2085 (1996).

In particular, compound VI, when administered daily by oral route to Wistar rats, dissolved in sesame oil at the concentration of 2 mg/mL , at the dose of 1mg/kg, did show a good activity in favouring colon ulcers repair, in re-establishing the normal thickness of the intestinal wall and in decreasing the granulocytes infiltration proper of an inflammatory condition.

Studies of acute and sub-acute toxicity were carried out on compound XIII, the results are herewith reported. The studies, carried out in different rodent and non rodent animal species, showed that at the effective doses, the therapeutic index is extremely favourable.

TABLE 2 -

ACUTE TOXICITY VALUES IN MICES, RATS AND HAMSTER TREATED BY PARENTERAL ROUTE

ANIMAL SPECIES	ADMINISTRATION ROUTE	DL 50 (mg/kg)
Mice	subcutaneous	3910
S.D. Rats	subcutaneous	3190
S.D. Rats	intramuscolar	>2000
Sirian hamster	subcutaneous	>2000
recovery	0	2

In S.D. rats administered daily for 20 consecutive days by subcutaneous route doses of 3, 6 and 10 mg/kg no toxic effects were observed on hepatic, hematopoietic and renal functions. A mild and transient effect on the body weight increase, was recorded at the higher dose. Similarly, the hepatic, hematopoietic and renal functions.were not altered in cynomolgus monkeys and in

baboons given daily for 5 consecutive days by intramuscular route doses up to 7.5 mg/kg.

Mutagenicity studies carried out in vitro and in vivo: the Ames test performed in strains of Salmonella typhimurium (up to 5 mg/mL), the chromosome aberration test performed in lung cells of Chinese hamster (up to 10^{-7}M), the micronucleous test performed in bone marrow cells of mouse (up to 600 mg/kg, s.c.) did show for compound XIII, complete lack of mutagenic potential.

Studies of general pharmacology, carried out in Beagle dogs, did not show effects on the cardiovascular system up to a daily intramuscular dose of 4 mg/kg given for 15 consecutive days.

Compound XIII, administered intramuscularly to S.D. rats at the daily dose of 40 mg/kg for 5 consecutive days, induced a slight decrease of the spontaneous motor activity, of curiosity and of the muscular tone.

Taking into account that in the therapy of psoriasis, at the active doses (cream 0.05-0.1%, i.e. 0.5-1 mg/g) the maximum applicable amount by epicutaneous route (whole body surface) as cream formulation is of about 50 g, i.e. 25-50 mg, and that the percutaneous absorption is about 10% of the applied dose, the maximum systemically bioavailable dose should be lower than 0.05-0.1 mg/kg.

These data confer to the product, when administered according to the therapeutic regimens studied (1/die for 7 consecutive days), a high safety of use.

Nitrogen heterocyclic aromatic derivatives of formula I and IV, when used according to the present invention, are advantageously prepared, as active principles, in pharmaceutical formulations for topical use, so to be administered, for example, by epicutaneous, oral and rectal route.

In the event of dermatological diseases derivatives object of the present invention, can also be advantageously prepared in pharmaceutical formulations suitable for transdermic application.

Mentioned pharmacutical preparations are properly formulated by employing, for example, proper transdermic release systems, particularly useful for the epicutaneous dosing, or are formulated in lipid vehicles (creams or ointments).

For example, as vehicles for the epicutaneous administration, can be advantageously used oils of vegetable origin or esters of fatty acids as sesame oil, maize seeds oil, corn oil, peanut oil, cotton seed oil, and ethyl oleate.

Other oily vehicles may as well be used provided that they are safe in the volume administered and do not interfere with the therapeutic efficacy of the preparation. As known to the art skilled man, these

preparations may also contain anti-microbial agents, to prevent growth of micro-organisms in the preparation, and antioxidants, essentially to prevent the development of rancidity of the oily vehicle.

Always as example, the optimal dose contains, on the average, from 0.01 to o.5% (w/w) of at least one derivative of the present invention of formula I and IV, as active principle, moreover for each product the optimal dose depends on the application area of the patient to be administered.

Is hereafter reported as example 11 a type formulation, referring to a cream useful for the treatment of psoriasis according to the present invention, which contains compound XIII as active principle.

EXAMPLE 11

100 mg of cream containing:

Compound (XIII)	100.0 mg
Crodabase PC-M	10.24g
Cetylic Alcohol	5.37g
liquid semi-synthetic trygliceride	8.51g
dymeticone	1.70g

paraseptics	0.15g
sweet almond oil	2.80g
stearine (stearic acid)	0.97g
propylen glycol	4.26g
tetra-sodic EDTA	0.14g
carbomer (carboxy-vinylpolymer)	0.16g
triethanolamine 99%	0.10g
depurated water (to 100g)	65.5g

Crodabase PC-M is a product of Croda Company , whose claimed composition is as follows: C 8-18 Acid POE, 3 C 6-22 alcohol ester and 0 6-22 alcohol.

Dealing with the oral administration in the therapy of ulcerous cholitis, are advantageously used gastro-protected controlled-release capsules (pH dedendent) containing lyposom preparations and/or lipids entrapping the active principle, which warrant the release at the site of action (colon).

Analogously , for the rectal administration, the use of foams containing lipid bases and appropriate surfactants can be useful in the treatment of the diseases of the low intestine.

EXAMPLE 12

Brief description of controlled release systems.

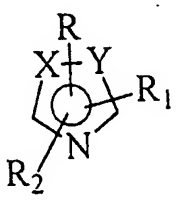
Gastro-protected capsules, pH dependent, containing a powder of lyophilised pre-lyposoms.

COMPOUND	RELATIVE AMOUNTS
Active principle	25 mg
Cholesterol	10 mg - 50 mg
Phospholipids*	30 mg - 150 mg

(*) = Phospholipids hydrogenated by soia oil

CLAIMS

1.Use of nitrogen heterocyclic aromatic derivatives having the following general formula:



(I)

where:

-when X=Y, X, Y=N;

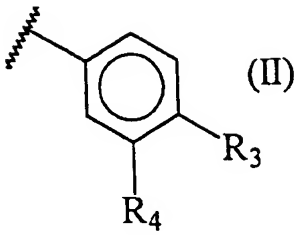
-when X≠Y, X, Y=N, C, CH;

-R is chosen between hydrogen, any other group able to form a bond with a nitrogen atom

$-COR_8$ where R_8 is C_1-C_{10} alkyl, C_2-C_4 alkenyl, C_2-C_4 alkinyl, phenyl possibly substituted by 1 to 3 substituents, benzyl, C_1-C_4 alkylamino, di-(C_1-C_4 alkyl)amino, phenylamino possibly substituted by 1 to 3 substituents, C_1-C_4 halolkyl, C_1-C_4 alkoxy, benzyloxy. Each eventual substituent being independently chosen among: halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoro-methyl, CN, nitro, amino, di-(C_1-C_4- alkyl)amino, acyl-aminoC_2-C_4 and methylendioxy;

SO_2R_{12}, where R_{12} is chosen among: C_1-C_4 alkyl, phenyl, (C_1-C_4 alkyl)phenyl, (C_1-C_4 alkoxy)phenyl, acetyl-phenyl;

- R_1 has the following general formula:



where R_3 and R_4 are independently chosen among:

hydrogen,

halogen,

C_1-C_{10} alkyl or alkoxyl C_1-C_{10},

allyloxy, propergyloxy,

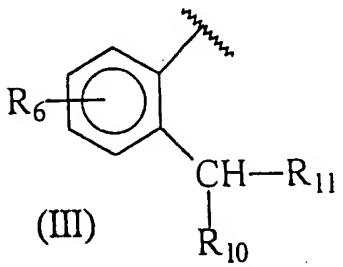
trifluoro-methyl,

phenyl,

di-methylamino,

or R_3 and R_4 together form a methylendioxy group;

- R_2 has the following general structure:



(III)

where R_6 is chosen among:

hydrogen,

halogen,

C_1-C_{10} alkyl or alkoxyl C_1-C_{10};

where R_{10} is chosen among:

hydrogen,

methyl;

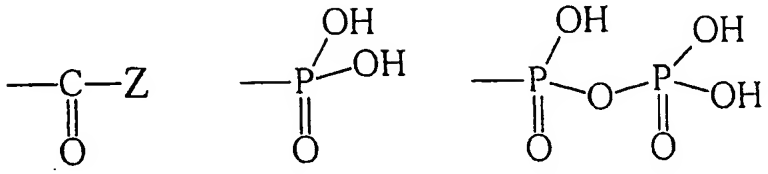
where R_{11} is chosen among:

hydrogen,

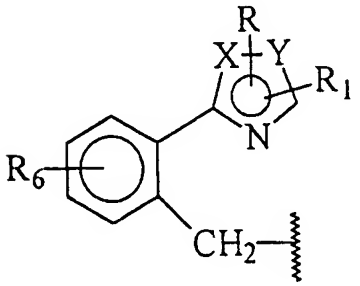
C_1-C_4 alkyl,

formyl,

OR_5, where R_5 is chosen among hydrogen, C_1-C_4 alkyl, SO_2R_{11}, where R_{11} is defined as above, or R_5 is chosen among:



where $Z=OR_7$ with R_7 is chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, or is chosen according to the following formula:



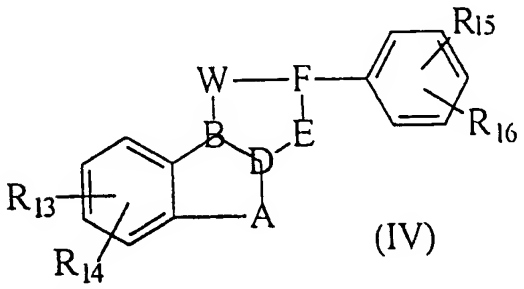
(XII)

where R, R_6, R_1, X and Y are defined as above or Z is chosen among.C_1-C_{20} linear or branched alkyl, C_2-C_4 alkenyl, C_2-C_4 alkinyl, phenyl possibly substituted by 1 to 3 substituents, benzyl, C_1-C_4 alkylamino, di-(C_1-C_4 alkyl)amino, phenyl-amino possibly substituted by 1 to 3 substituents, C_1-C_4 halo-alkyl, C_1-C_4 alkoxy, benzyloxy. Each eventual substituent being independently chosen among: halogen, C_1-C_4

alkyl, C_1-C_4 alkoxy, trifluoro-methyl, CN, nitro, amino, of(C_1-C_4 alkyl)amino, acyl-aminoC_2-C_4 and methylendioxy; or Z is chosen equal to NHR_9 where R_9 is an alkenyl chain C_1-C_{20}, linear or branched, otherwise named R_{10} and R_{11} together represent a further bond between carbon and oxygen atom,

mentioned R_1 and R_2 are never located on two adjacent atoms of the heterocyclic aromatic ring;

or by nitrogen heterocyclic aromatic derivatives of general formula as follows:



(IV)

where R_{15} and R_{16} are chosen among

hydrogen,

halogen,

C_1-C_4 alkyl or alkoxyl C_1-C_4;

C_3-C_5 alkyl or alkoxyl C_3-C_5;

cycloalkyloxyl C_3-C_6

benzyloxy

halogen,

or chosen ensemble R_{15} and R_{16} represent a methylendioxy group;

R_{13} and R_{14} are chosen among

hydrogen,

halogen,

C_1-C_4 alkoxyl

- A is chosen as

-CH_2- -CH=CH-, -CH_2CH_2-, -$(CH_2)_3$; -CH_2S-

-B is chosen as C, N

-D is chosen as C, N

or B and D together are equal to C=C;

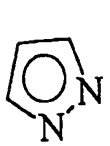
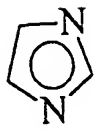
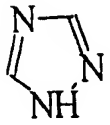
-E is chosen as N, C, CO, NH, CH, NR_{17} , CR_{17} where R_{17} is chosen as linear C_1-C_4 alkyl

-F is chosen as CH, N

-W is chosen as: N, NH, CH, NR_{17}, CR_{17}, CR_{18}, where CR_{17} is defined as above and R_{18} is chosen as carboxy, carbo(C_1-C_4 alkyl), carbamyl, mono or di-(C_1-C_4 alkyl)carbamyl, hydroxymethyl;

The mentioned derivatives of general formulas (I) and (IV) being used in the topical pharmacological treatment of diseases of epithelial tissues.

2.Use of nitrogen heterocyclic aromatic derivatives according to the claim 1. Where, the mentioned nitrogen heterocyclic aromatic derivative of formula (I) is a derivative of pyrazole, imidazole and 1H-1, 2, 4-triazole respectively:

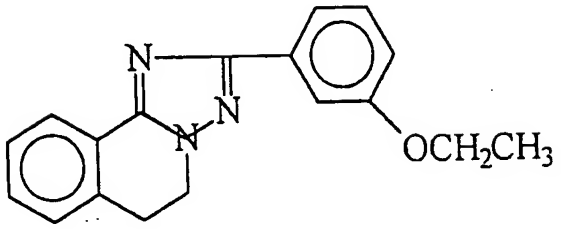
3. Use of nitrogen heterocyclic aromatic derivatives according to the claim 1. where, for the mentioned derivative of general formula (IV), R_{13} and R_{14} is hydrogen, A is chosen among $-CH_2-$, $-CH=CH-$, $-CH_2-CH_2-$; D is chosen as N, B is chosen equal to C, W is chosen as N, R_{15} is hydrogen, and R_{16} is chosen between C_1-C_4 alkoxy and phenyl.

4. Use of nitrogen heterocyclic aromatic derivatives according to the claim 1., where according to the present invention are advantageously used in the topic treatment of the diseases of the epithelial tissues, like the psoriasis and atopic dermatitis.

5. Use of nitrogen heterocyclic aromatic derivatives according to the claim 1., where according to the present invention are advantageously used in the topic treatment of the diseases of the epithelial tissues, like the ulcerous cholitis and the Crohn illness

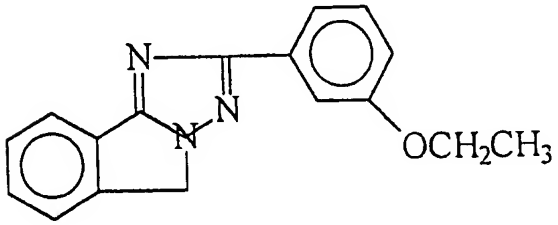
6. Use of nitrogen heterocyclic aromatic derivatives according to claim 1, where the mentioned derivative

of general formula (IV) has the following chemical structure:



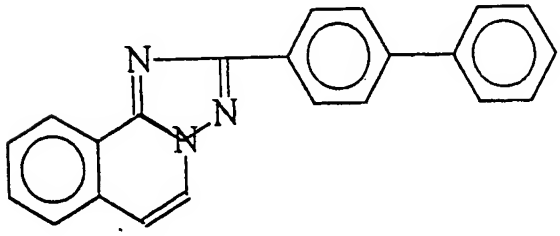
(X)

7. Use of nitrogen heterocyclic aromatic derivatives according to claim 1, where the mentioned derivative of general formula (IV) has the following chemical structure:



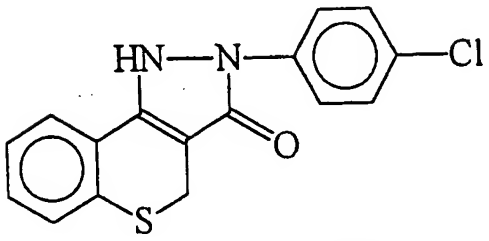
(XI)

8. Use of nitrogen heterocyclic aromatic derivatives according to claim 1, where the mentioned derivative of general formula (IV) has the following chemical structure:



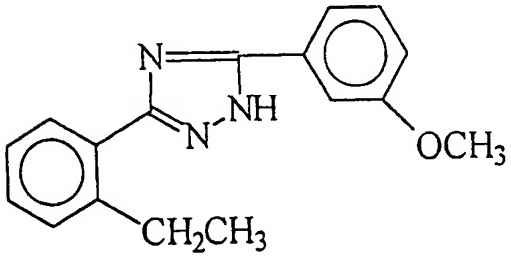
(XII)

9.Use of nitrogen heterocyclic aromatic derivatives according to claim 1, where the mentioned derivative of general formula (IV) has the following chemical structure:



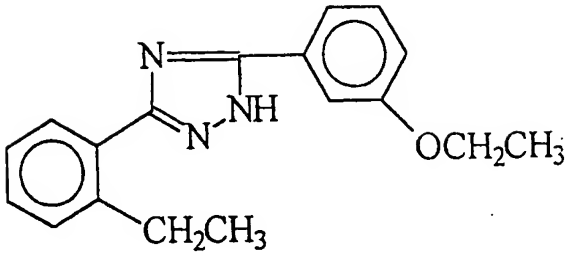
(XIV)

10.Use of nitrogen heterocyclic aromatic derivatives according to claim 1, where the mentioned derivative of general formula (IV) has the following chemical structure:



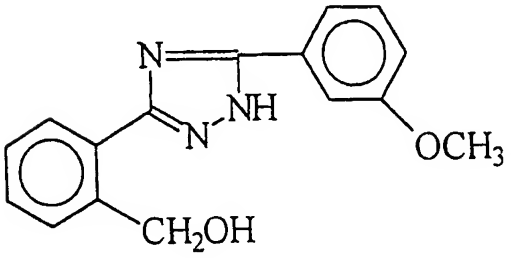
(XIII)

11.Use of nitrogen heterocyclic aromatic derivatives according to claim 1, where the mentioned derivative of general formula (IV) has the following chemical structure:



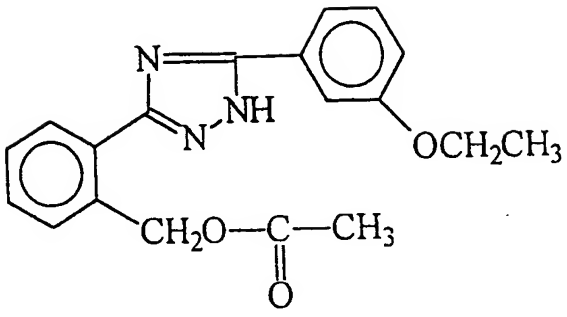
(V)

12. Use of nitrogen heterocyclic aromatic derivatives according to claim 1, where the mentioned derivative of general formula (IV) has the following chemical structure:



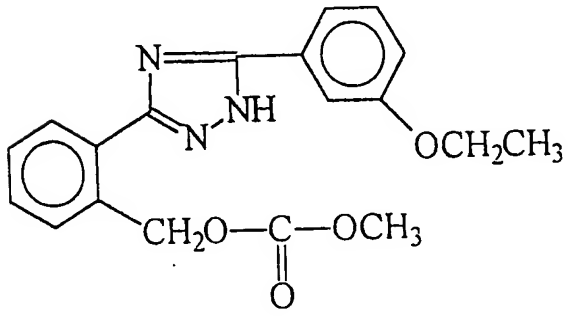
(VI)

13. Use of nitrogen heterocyclic aromatic derivatives according to claim 1, where the mentioned derivative of general formula (IV) has the following chemical structure:



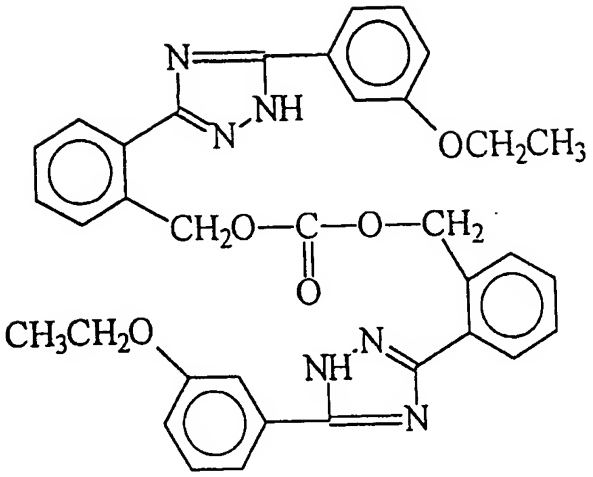
(VII)

14. Use of nitrogen heterocyclic aromatic derivatives according to claim 1, where the mentioned derivative of general formula (IV) has the following chemical structure:



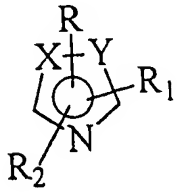
(VIII)

15. Use of nitrogen heterocyclic aromatic derivatives according to claim 1, where the mentioned derivative of general formula (IV) has the following chemical structure:



(IX)

16.Nitrogen heterocyclic aromatic derivatives having the following general formula:



(I)

where:

-when X=Y, X,Y=N;

-when X=Y, X,Y=N, C, CH;

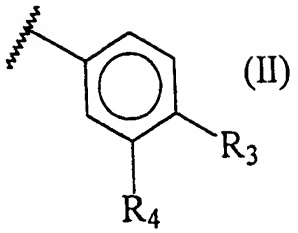
-R is chosen among:

hydrogen,

any group able to form a bond with a nitrogen atom,

$-COR_8$ where R_8 is a saturated or non-saturated C_1-C_{10} aliphatic hydrocarbon;

.-R_1 has the following general structure:



(II)

where:

R_3 and R_4 independently between them, are chosen among

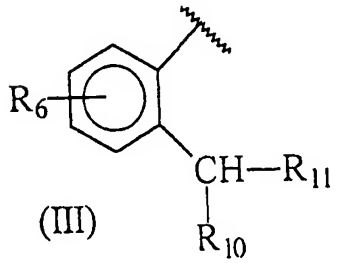
hydrogen,

halogen,

C_1-C_{10} alkyl or alkoxyl C_1-C_{10},

or R_3 and R_4 together form a methylendioxy group;

.-R_2 has the following general structure:



(III)

where R_6 is chosen among:

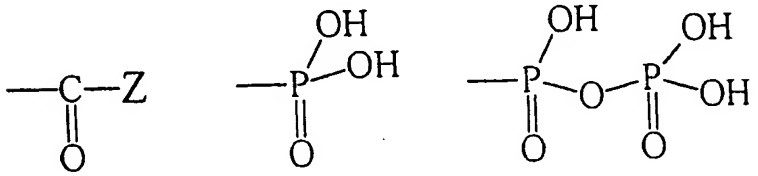
hydrogen,

halogen,

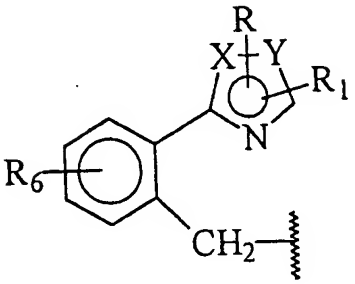
C_1-C_{10} alkyl or C_1-C_{10} alkoxyl;

where R_{10} is chosen as hydrogen,

where R_{11} is chosen as:OR_5, where R_5 is chosen among C_1-C_{20} saturated or non-saturated, linear or branched aliphatic hydrocarbon, or R_5 is chosen among:



where $Z=OR_7$ with R_7 chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, or is chosen according to the following formula:

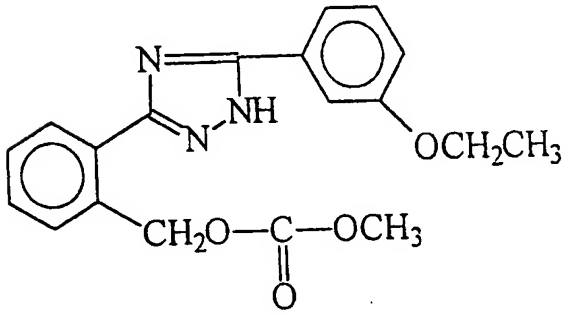


(XII)

where R, R_1, R_6, X and Y are defined as above or Z is chosen equal to NHR_9 where R_9 is a C_1-C_{20} linear or branched alkyl chain.

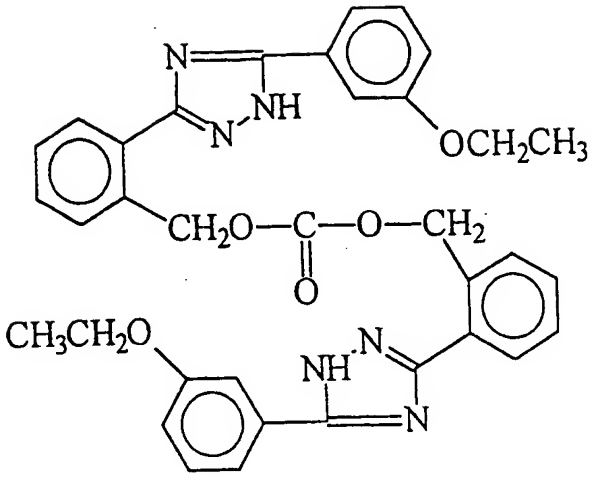
Mentioned R_1 and R_2 being never located on two adjacent atoms of the heterocyclic aromatic ring.

17.Nitrogen heterocyclic aromatic derivative according to claim 16,, having the following general formula:



(VIII)

18.Nitrogen heterocyclic aromatic derivative according to claim 16,, having the following general formula:



(IX)

19. Use of nitrogen heterocyclic aromatic derivatives according to the claim 1., by topical administration by epicutaneous route

20. Use of nitrogen heterocyclic aromatic derivatives according to the claim 1, by local administration by oral route

21. Use of nitrogen heterocyclic aromatic derivatives according to the claim 1, by local administration by rectal route

22. Use of nitrogen heterocyclic aromatic derivatives according to the claim 1, in combination with known drugs usually used in the treatment of epithelial tissues.

23. Pharmaceutical preparation which contains, as active principle, at least one nitrogen heterocyclic aromatic derivative used according to claim 1, for the topical treatment of the epithelial tissues diseases.

24. Pharmaceutical preparation according to claim 23, for the topical treatment of dermatological diseases. as psoriasis and atopic dermatitis.

25. Pharmaceutical preparation according to claim 23, for the topical treatment of the diseases of the epithelial tissues of the low intestine, like the ulcerous cholitis and the Crohn illness

26. Pharmaceutical preparation according to claim 25, formulated as gastro-protected, controlled release capsules

27. Pharmaceutical preparation according to claim 24, formulated using appropriate systems suitable for a transdermic release.

28. Pharmaceutical preparation according to claims 23 and 25, formulated using lipid vehicles .

29. Pharmaceutical preparation according to claims 28, where the mentioned lipid vehicles are chosen among oils of vegetable origin esters of fatty acids as sesame oil, maize seeds oil, corn oil, peanut oil, cotton seed oil, and ethyl oleate.

30. Pharmaceutical preparations according to claims 23 and 29 which contain known anti-microbial agents,

31. Pharmaceutical preparations according to claims 23 and 29 which contain known anti-oxidant agents

32. Pharmaceutical preparations, according to claims 23 and 29, containing 0.01% to 0.5% (w/w) of at least on derivative of formulas (I) and or (IV), used according to claim I as active principle,

33. Pharmaceutical preparation, according to claims 23 containing in 100 g:

Compound (XIII)	100.0 mg
Crodabase PC-M	10.24g
Cetylic Alcohol	5.37g
liquid semi-synthetic tryglicerides	8.51g
dymeticone	1.70g

paraseptics	0.15g
sweet almond oil	2.80g
stearine (stearic acid)	0.97g
propylen glycol	4.26g
tetra-sodic EDTA	0.14g
carbomer (carboxy-vinylpolymer)	0.16g
triethanolamine 99%	0.10g
depurated water (to 100g)	65.5g

34. Procedure for the preparation of derivatives of claim 16 which includes the following phases:

-preparation of an alcoholate and of an imidazolide starting from the corresponding alcohol,

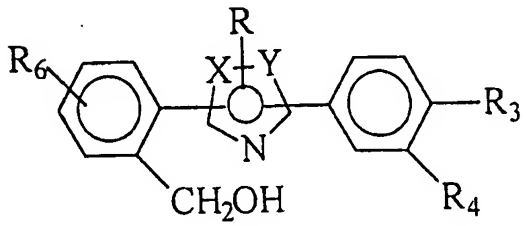
-Mixing of the mentioned alcoholate and imidazolide, giving rise to a symmetric or asymmetric carbonate.

35. Procedure according to claim 34, utilising for the preparation of the alcoholate catalytic or stoichiometric amounts of NaH or metallic sodium, with a temperature between 0 and 60°C and a reaction time between 30 min and 12 hours.

36. Procedure according to claim 34, utilising for the mixing phase a temperature between 10 and 60°C and a reaction time between 6 and 24 hours

37. Procedure for the preparation of derivatives of claim 16 which includes the following phases:

-preparation of a nitrogen heterocyclic aromatic derivative of general formula:



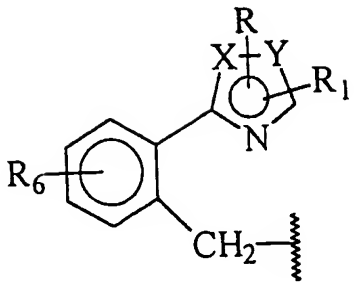
(XV)

-possible protection of the -OH group, possible acylation reaction with introduction of a $-COR_8$ group and formation of an acylated derivative, subsequent de-protection of the -OH group,

and therefore alternatively:

-reaction of derivative (XV) with a carbonating agent, to form the corresponding carbonate,

-reaction of the mentioned carbonate with a derivative Z where $Z=OR_7$ with R_7 chosen among saturated or non-saturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, or chosen according to the following formula:



(XII)

-where R, R_1, R_6, X and Y are defined as above,or Z is chosen equal to NH-R_9 where R_9 is a linear or branched C_1-C_{20} alkyl chain, with formation of the mentioned derivative of formula (I),

or:

-reaction of the mentioned derivative (XV) with phosphoric acid or related products, with formation of the mentioned derivative of formula (I),

38.- Procedure for the preparation of derivatives of claim 37, taking into consideration that the carbonating agent is phosgene ($COCl_2$)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/41, C07D 249/08, 249/16, 249/22 | A3

(11) International Publication Number: **WO 98/55118**

(43) International Publication Date: 10 December 1998 (10.12.98)

(21) International Application Number: PCT/EP98/03497

(22) International Filing Date: 4 June 1998 (04.06.98)

(30) Priority Data:
MI97A001329 5 June 1997 (05.06.97) IT

(71) Applicant *(for all designated States except US)*: IRILAB LTD. [IE/IE]; Merchant's House, 27/30 Merchant's Quay, Dublin 8 (IE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: ROSSI, Carla [IT/IT]; Via Cadore, 15, I–20135 Milano (IT).

(74) Agent: TRUPIANO, Roberto; Brevetti Europa S.r.l., Piazza Bernini, 6, I–20133 Milano (IT).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
15 April 1999 (15.04.99)

(54) Title: USE OF NITROGEN HETEROCYCLIC AROMATIC DERIVATIVES IN THE TOPICAL TREATMENT OF THE EPITHELIAL TISSUES DISEASES

(57) Abstract

Derivatives of general chemical formula (I) and (IV) are advantageously used in the topic treatment of the diseases of the epithelial tissues, like the psoriasis (epidermis) and the ulcerous cholitis (low intestine). The mentioned derivatives display a high efficacy when administered for example by epicutaneous route in the case of dermatological illnesses like the psoriasis, atopic dermatitis and other similar affections, or when administered by oral or for example by rectal route in the case of diseases of the epithelia of the low intestine like the ulcerous cholitis and the Crohn.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/03497

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/41 C07D249/08 C07D249/16 C07D249/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 43 20 801 A (FAHLBERG LIST PHARMA GMBH) 5 January 1995 see page 3; table 1 see claims 1-3 ---	1,2,4,5, 10-38
Y	WO 94 17068 A (BRITISH TECH GROUP ;ALBRECHTSEN STEN (DK); HANSEN JENS (DK); LANGV) 4 August 1994 see claims 1-14 ---	1,2,4,5, 10-38
X	EP 0 011 129 A (LEPETIT SPA) 28 May 1980 see page 14, line 9-12; claims 1-7 ---	16-18, 23-38
A	EP 0 080 053 A (LEPETIT SPA) 1 June 1983 cited in the application see claims 1-8 --- -/--	1,2,4,5, 10-38

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1998	26.02.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seegert, K

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/03497

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 29 43 326 A (LEPETIT SPA) 14 May 1980 see page 57, line 19-20; claims 1-12	16-18, 34-38
A	US 4 379 155 A (OMODEI-SALE AMEDEO ET AL) 5 April 1983 see claims 1-9	1,2,4,5, 10-38
Y	MISTRELLO G. ET AL: "Immunological Profile of DL111-IT, a New Immunosuppressant Agent" IMMUNOPHARMACOLOGY, vol. 10, 1985, pages 163-169, XP002082252 see abstract	1,2,4,5, 10-38
Y	"Pschyrembel Klinisches Wörterbuch" 1994 , WALTER DE GRUYTER , BERLIN NEW YORK XP002082253 "Autoimmunkrankheiten" see page 142	1,2,4,5, 10-38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/03497

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,2,4,5,10-38

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1,2,4,5,10-38

Use of nitrogen heterocyclic aromatic derivatives according to formula (I) for the topical pharmacological treatment of diseases of the epithelial tissue (respective parts of claims 1,2,4,5,10-15,19-22), nitrogen heterocyclic aromatic derivatives according to the general formula (I) as disclosed in claims 16 - 18, pharmaceutical compositions comprising compounds of formula (I) (respective parts of claims 23 - 33) and a process for making these compounds (respective parts of claims 34 - 38)

2. Claims: 1-9,19-32

Use of nitrogen heterocyclic aromatic derivatives according to formula (IV) for the topical pharmacological treatment of diseases of the epithelial tissue (respective parts of claims 1-9,19-22) and pharmaceutical compositions comprising compounds of formula (IV) (respective parts of claims 23 - 32)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/03497

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4320801 A	05-01-1995	NONE	
WO 9417068 A	04-08-1994	AU 5891294 A	15-08-1994
		GB 2278842 A	14-12-1994
		SE 9300127 A	20-07-1994
		ZA 9400382 A	19-07-1995
EP 0011129 A	28-05-1980	AT 383 T	15-11-1981
		BE 879727 A	30-04-1980
		CH 649082 A	30-04-1985
		FR 2440363 A	30-05-1980
		GB 2034710 A,B	11-06-1980
		JP 1448464 C	11-07-1988
		JP 55062076 A	10-05-1980
		JP 62058354 B	05-12-1987
		US 4409388 A	11-10-1983
EP 0080053 A	01-06-1983	AT 18399 T	15-03-1986
		AU 557034 B	04-12-1986
		AU 8886382 A	28-04-1983
		CA 1181406 A	22-01-1985
		IE 54052 B	24-05-1989
		JP 1634484 C	20-01-1992
		JP 2061949 B	21-12-1990
		JP 58079984 A	13-05-1983
		US 4535090 A	13-08-1985
		ZA 8207172 A	31-08-1983
DE 2943326 A	14-05-1980	AT 368754 B	10-11-1982
		AT 697279 A	15-03-1982
		AU 533727 B	08-12-1983
		AU 5205379 A	08-05-1980
		BE 879732 A	30-04-1980
		CA 1116610 A	19-01-1982
		CH 642953 A	15-05-1984
		DK 456779 A,B,	01-05-1980
		FI 793216 A,B,	01-05-1980
		FR 2440364 A	30-05-1980
		GB 2039887 A,B	20-08-1980
		GR 69857 A	19-07-1982
		HK 37183 A	30-09-1983
		IE 49626 B	13-11-1985
		JP 1047469 B	13-10-1989
		JP 1560238 C	31-05-1990
		JP 55062075 A	10-05-1980
		LU 81832 A	07-05-1980
		NL 7907913 A	02-05-1980
		SE 445453 B	23-06-1986
		SE 7908940 A	01-05-1980
		US 4459302 A	10-07-1984
		US 4888350 A	19-12-1989
		ZA 7905798 A	26-11-1980
US 4379155 A	05-04-1983	US 4370336 A	25-01-1983